MicroRNA miR-425 is a negative regulator of atrial natriuretic peptide

BMC Pharmacology & Toxicology

ORAL PRESENTATION Open Access

MicroRNA miR-425 is a negative regulator of atrial natriuretic peptide

Pankaj Arora[1,2,3,4], Connie Wu[5], Donald B Bloch[6,7], Brandi N Davis-Dusenbury[8], Ester Spagnolli[5], Akiko Hata[9], Sara Vandenwijngaert[10], Melissa Swinnen[10], Stefan Janssens[10], Emmanuel S Buys[5], Kenneth D Bloch[1,2,5*†], Christopher Newton-Cheh[1,2,3,4†], Thomas J Wang[1,2†]

From 6th International Conference on cGMP: Generators, Effectors and Therapeutic Implications
Erfurt, Germany. 28-30 June 2013

Background

Numerous common genetic variants have been linked to blood pressure, but no underlying mechanism has been elucidated. Population studies have revealed that a genetic variant, rs5068 (A/G), is associated with blood pressure and the risk of hypertension. rs5068 lies in the 3' untranslated region (3'UTR) of *NPPA*, the gene encoding atrial natriuretic peptide (ANP), and presence of the minor G allele is associated with increased circulating ANP levels and reduced blood pressure.

Results

We hypothesized the existence of a microRNA (miR) that targets the *NPPA* 3'UTR and that the binding of the miR to the NPPA 3'UTR would be disrupted in transcripts from the rs5068 minor allele. We identified a microRNA, miR-425, that is predicted to bind the sequence spanning rs5068 for the A, but not the G, allele. miR-425 is expressed in human atria and ventricles. Using luciferase-3'UTR reporter constructs, we observed that miR-425 could silence reporter mRNAs carrying the *NPPA* major allele 3'UTR, but not those carrying the minor allele 3'UTR. Similarly, an anti-miR directed against miR-425 augmented expression of the luciferase-NPPA 3'UTR construct containing the major allele but not the minor allele. miR-425 reduced NPPA mRNA levels and ANP synthesis in human cardiomyocytes derived from induced pluripotent stem cells.

Conclusion

Our studies provide mechanistic insights into how a common genetic variant identified in population genetic studies can regulate ANP levels and blood pressure. miR-425 is a novel regulator of ANP production, raising the possibility that miR-425 antagonists could be used to treat disorders of salt overload, including hypertension and heart failure.

Authors' details
[1]Cardiology Division, Massachusetts General Hospital, Boston, Massachusetts, USA. [2]Cardiovascular Research Center, Massachusetts General Hospital, Boston, Massachusetts, USA. [3]Center for Human Genetic Research, Massachusetts General Hospital, Boston, Massachusetts, USA. [4]Program in Medical and Population Genetics, Broad Institute, Cambridge, Massachusetts, USA. [5]Department of Anesthesia, Critical Care, and Pain Medicine, Massachusetts General Hospital, Boston, Massachusetts, USA. [6]Division of Rheumatology, Allergy, and Clinical Immunology, Massachusetts General Hospital, Boston, Massachusetts, USA. [7]Center for Immunology and Inflammatory Diseases, Massachusetts General Hospital, Boston, Massachusetts, USA. [8]Stem Cell and Regenerative Biology, Harvard University, Cambridge, Massachusetts, USA. [9]Cardiovascular Research Institute, University of California, San Francisco, CA, USA. [10]Department of Cardiovascular Sciences, Gasthuisberg University Hospital, University of Leuven, Belgium.

Published: 29 August 2013

doi:10.1186/2050-6511-14-S1-O10
Cite this article as: Arora *et al.*: MicroRNA miR-425 is a negative regulator of atrial natriuretic peptide. *BMC Pharmacology and Toxicology* 2013 **14**(Suppl 1):O10.

* Correspondence: kdbloch@partners.org
† Contributed equally
[1]Cardiology Division, Massachusetts General Hospital, Boston, Massachusetts, USA
Full list of author information is available at the end of the article